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**TRANSMITTAL
FORM**

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Total Number of Pages in This Submission

Application Number	10/519,110
Filing Date	July 2, 2003
First Named Inventor	Etcheberrigaray
Art Unit	Not Yet Assigned
Examiner Name	Not Yet Assigned
Attorney Docket Number	17357.01001US

ENCLOSURES (Check all that apply)

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|---|--|--|
| <input type="checkbox"/> Fee Transmittal Form
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1. Copies of 74 Cited References

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Milbank, Tweed, Hadley & McCloy LLP		
Signature			
Printed name	Einar Stole		
Date	3.28.05	Reg. No.	47,272

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I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	
)	
Rene Etcheberrigary <i>et al.</i>)	Group Art Unit: Not Yet Assigned
)	
Patent Application No. 10/519,110)	Examiner: Not Yet Assigned
)	
Filed: July 2, 2003)	
)	
For: <i>PKC Activation As A Means For</i>)	
<i>Enhancing sAPPα Secretion and</i>)	
<i>Improving Cognition Using Bryostatin</i>)	
<i>Type Compounds</i>)	

INFORMATION DISCLOSURE STATEMENT

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Sir:

In accordance with 37 C.F.R. §§ 1.97 and 1.98, and in compliance with the duty of disclosure set forth in C.F.R. § 1.56, applicants are submitting herewith copies of references listed on the attached Forms PTO/SB/08A and PTO/SB/08B for consideration and to be made of record herein by the U.S. Patent and Trademark Office in the above-captioned application.

Consideration of the foregoing plus the prompt return of a copy of the enclosed Forms PTO/SB/08A and PTO/SB/08B with the Examiner's initials in the left column in accordance with MPEP 609 are respectfully requested.

Applicants' submission of the Information Disclosure Statement (IDS) shall not be construed as an admission that the cited references are prior art to the present invention, or that the cited references qualify as printed publications. The submission of this IDS also shall not be construed as a representation that a prior art search has been performed.

In accordance with 37 C.F.R. § 1.97(b), this Information Disclosure Statement is believed to be submitted before the mailing of a first Official Action. Therefore, it is respectfully submitted that no fee is required for consideration of this information. However, in any event any fee is deemed necessary,

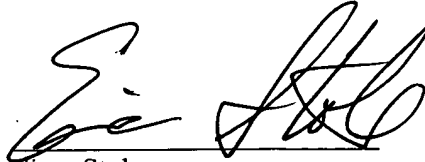
the Commissioner is authorized to charge the undersigned's Deposit Account No. 13-3250 under referenced No. 17357.01001US.

Respectfully submitted,

MILBANK, TWEED, HADLEY & McCLOY LLP

Date: March 28, 2005

By:

A handwritten signature in black ink, appearing to read 'Einar Stole', written over a horizontal line.

Einar Stole

Registration No. 47,272

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet

1

of

1

1

Complete if Known

Application Number	10/519 110
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Filing Date	July 2, 2003
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First Named Inventor	Etcheberrigaray
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Art Unit	Not Yet Assigned
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Examiner Name	Not Yet Assigned
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Attorney Docket Number	17357.01001US
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U. S. PATENT DOCUMENTS

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FOREIGN PATENT DOCUMENTS

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Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ^o
		Country Code ³ Number ⁴ Kind Code ⁵ (if known)				
		JP 279311	03/26/1993			
		JP 240581	02/29/2000			
		JP 406279311A	10/04/1994	Tamura et al.		
		WO 2004/004641 A2	01/15/2004	Etcheberrigarary et al.		
		WO 97/43268	11/20/1997	Kozikowski		

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

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		Examiner Name	Not Yet Assigned
Sheet 2	of	Attorney Docket Number	17357.01001US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Alkon, D.L. et al. "Regulation of Hermissenda K ⁺ Channels by Cytoplasmic and Membrane-Associated C-Kinase," J. Neurochem., Vol. 51, No. 3, 1988	
		Bennett, Brian D., et al. "Expression Analysis of BACE2 in Brain and Peripheral Tissues," The Journal of Biological Chemistry, Vol. 275, No. 27, Issue of July 7, pp. 29647-20651, 2000	
		Bergamaschi, Stefania, et al. "Defective phorbol ester-stimulated secretion of B-amyloid precursor protein from Alzheimer's disease fibroblasts," Neuroscience Letters 201(1995) 1-4	
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		Burke, James R., et al. "Update on Alzheimer's Disease: Promising advances in detection and treatment," Postgraduate Medicine, Vol. 106, No. 5, October 15, 1999	
		Bury, Richard W. "PKC Activators (Phorbol Ester or Bryostatin) Stimulate Outgrowth of NFG-Dependent Neurites in a Subline of PC12 Cells," Journal of Neuroscience Research, 53:214-22 (199)	
		Buxbaum, Joseph D., et al. "Evidence That Tumor Necrosis Factor a Converting Enzyme is Involved In Regulated a-Secretase Cleavage of the Alzheimer Amyloid Protein Precursor," The Journal of Biological Chemistry, Vol. 273, No. 43, Issue of October 23, pp. 27765-27767, 1998	
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		Cole, Gregory, et al. "Decreased levels of protein kinase C in Alzheimer brain," Brain Research, 452 (1988) 165-174	

Examiner Signature	Date Considered
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		Examiner Name	Not Yet Assigned
		Attorney Docket Number	17357.01001US
Sheet	3	of	

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Connolly, Gerald P. "Fibroblast models of neurological disorders: fluorescence measurement studies," TIPS - May 1998 (Vol. 19)	
		Coughlan, Christine, et al. "Factors influencing the processing and function of the amyloid B precursor protein - a potential therapeutic target in Alzheimer's disease?," Pharmacology & Therapeutics 86 (2000) 111-144	
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		Efthimiopoulos, Spiros, et al. "Intracellular Cyclic AMP Inhibits Constitutive and Phorbol Ester-Stimulated Secretory Cleavage of Amyloid Precursor Protein," J. Neurochem. Vol. 67, No. 2, 1996	
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		Etcheberrigaray, Rene, et al. "Calcium responses are altered in fibroblasts from Alzheimer's patients and pre-symptomatic PS1 carriers: a potential tool for early diagnosis," Research Report, Alzheimer's Report, Vol. 3, Nos. 5 & 6, pp. 305-312 (2000)	
		Favit, Antonella et al. "Alzheimer's-specific effects of soluble B-amyloid on protein kinase C- α and - γ degradation in human fibroblasts," Proc. Natl. Acad. Sci. USA Vol. 95, pp. 5562-5567, May 1998 Cell Biology	
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		Ghosh, Arun, et al. "Design of Potent Inhibitors for Human Brain Memapsin 2 (B-Secretase)," J. Am. Chem. Soc. 2000, 122, 3522-3523	

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		Goekjian, Peter G., et al. "Protein Kinase C in the Treatment of Disease: Signal Transduction Pathways, Inhibitors, and Agents in Development," Current Chemistry, 1999, 6, 877-903	
		Govoni, S., et al. "Fibroblasts of patients affected by Down's syndrome oversecrete amyloid precursor protein and are hypo-responsive to protein kinase C stimulation," Neurology 1996; 46:1069-1075	
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		Haniu, Mitsuru, et al. "Characterization of Alzheimer's B-Secretase Protein BACE," The Journal of Biological Chemistry, Vol. 275, No. 28, Issue of July 14, pp. 21099-21106, 2000	
		Hardy, John "Amyloid, the presenilins and Alzheimer's disease," TINS, Vol. 20, No. 4, 1997	
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		Hofmann, Johann "The potential for isoenzyme-selective modulation of protein kinase C," The FASEB Journal, Vol. 11, July 1997	
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		Huynh, Tuan Van, et al. "Reduced Protein Kinase C Immunoreactivity and Altered Protein Phosphorylation in Alzheimer's Disease Fibroblasts," Arch Neurol - Vol. 46, November 1999	
		Ibarreta, Dolores, et al. "Benzolactam (BL) enhances sAPP secretion in fibroblasts and in PC12 cells," NeuroReport 10, 1035-1040 (1999)	

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		Jin, Lee-Way, et al. "Changes in Protein Kinases in Brain Aging and Alzheimer's Disease," Drugs & Aging, 6(2) 1995	
		Jolly-Tornetta, Camille, et al. "Protein Kinase C Regulation of Intracellular and Cell Surface Amyloid Precursor Protein (APP) Cleavage in CHO695 Cells," Biochemistry 2000, 39, 15282-15290	
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		Kinouchi, Tadatoshi et al. "Conventional protein kinase C (PKC)-a and novel PKCe, but not -s, increase the secretion of an N-terminal fragment of Alzheimer's disease amyloid precursor protein from PKC cDNA transfected 3Y1 fibroblasts," FEBS Letters 364 (1995) 203-206	
		Kozikowski, Alan P., et al. "Modeling, Chemistry, and Biology of the Benzolactam Analogues of Indolactam V (ILV). 2. Identification of the Binding Site of the Benzolactams in the CRD2 Activator-Binding Domain in PKCs and Discovery of an ILV Analogue of Improved Isozyme Selectivity," J. Med. Chem. 1997, 40, 1316-1326	
		Maiorini, A.F., et al. "Potential novel targets for Alzheimer pharmacotherapy: I. Secretase," Journal of Clinical Pharmacy and Therapeutics (2002) 27, 169-183	
		Masilah, E., et al. "Protein Kinase C Alteration Is An Early Biochemical Marker In Alzheimer's Disease," The Journal of Neuroscience, September 1991, 11(9): 2759-2676	
		Masilah, Eliezer "Role of Amyloid Precursor Protein in the Mechanisms of Neurodegeneration in Alzheimer's Disease," Laboratory Investigation, September 1997, Vol. 77, No. 3, p. 197	
		Hardy, J. "Molecular genetics of Alzheimer's disease," Acta Neurol Scand 1996: Supplement 165: 13-17	
		Mutter, Roger et al. "Chemistry and Clinical Biology of the Bryostatins," Bioorganic & Medicinal Chemistry 8 (2000) 1841-1860	

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		Nan, Fajun et al. "Dual Function Glutamate-Related Ligands: Discovery of a Novel, Potent Inhibitor of Glutamate Carboxypeptidase II Possessing mGluR3 Agonist Activity," Journal of Medicinal Chemistry, 43 (5): 772-774	
		Neurology of Disease. Experimental Neurology, Part B, Vol. 5, No. 3, September 1998	
		RobNer, S., et al. "Short Communication. Protein kinase Ca and B1 isoforms are regulators of a-secretory proteolytic processing of amyloid precursor protein in vivo," European Journal of Neuroscience, Vol. 13, pp. 1644-1648, 2001	
		Savage, Mary J., et al. "Turnover of Amyloid B-Protein in Mouse Brain and Acute Reduction of Its Level by Phorbol Ester," The Journal of Neuroscience, March 1, 1998, 18(5): 1743-1752	
		Scheuner, D., et al. "Secreted amyloid B-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease," Nature Medicine, Vol. 2, No. 8, August 1996	
		Selkoe, Dennis J. "Alzheimer's Disease: Genes, Proteins, and Therapy," Pharmacological Review, Vol. 81, No. 2, April 2001	
		Selkoe, Dennis J. "Normal and Abnormal Biology of the B-Amyloid Precursor Protein," Annu. Re. Neurosci. 1994, 17:489-517	
		Selkoe, Dennis J. "Translating cell biology into therapeutic advances in Alzheimer's disease," Nature, Vol. 399, Supp. 34 June 1999	
		Shimohama, S., et al. "Assessment of protein kinase C isozymes by two-site enzyme immunoassay in human brains and changes in Alzheimer's disease," Neurology 1993: 43:1407-1413	
		Shoulson, Ira "Experimental Therapeutics of odenegenerative Disorders: Unmet Needs," Science, Vol. 282, 6 November 1998	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>		Complete if Known	
		Application Number	10/519,110
		Filing Date	July 2, 2003
		First Named Inventor	Etcheberrigaray
		Art Unit	Not Yet Assigned
		Examiner Name	Not Yet Assigned
Sheet 7	of	Attorney Docket Number	17357.01001US

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Sinha, Sukanto et al. "Purification and cloning of amyloid precursor protein B-secretase from human brain," Nature, Vol. 402, 2 December 1999	
		Skovronsky, Daniel M., et al. "Protein Kinase C-dependent a-Secretase Competes with B-Secretase for Cleavage of Amyloid- B Precursor Protein in the Trans-Golgi Network," The Journal of Biological Chemistry, Vol. 275, No. 4, Issue of January 28, pp. 2568-2575, 2000	
		Small, David H., et al. "Alzheimer's Disease and the Amyloid B Protein: What Is The Role of Amyloid?" Journal of Neurochemistry, Vol. 73, No. 2, 1999	
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		Tanzi, Rudolph E., et al. "The Gene Defects Responsible for Familial Alzheimer's Disease," Neurology of Disease 3, 159-168 (1996) Article No. 0016	
		Turner, Robert T., et al. "Specificity of Memapsin 1 and Its Implications on the Design of Memapsin 2 (B-Secretase) Inhibitor Selectivity," Biochemistry 2002, 41, 8742-8746	
		Varterasian, Mary L., et al. "Phase II Trial of Bryostatin 1 in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia," Clinical Cancer Research, Vol. 6, 825-828, March 2000	
		Vassar, Robert et al. "AB-Generating Enzymes: Recent Advances in B- and y-Secretase Research, Neuron, Vol. 27, 419-422, September 2000	
		Vassar, Robert et al. "B-Secretase Cleavage of Alzheimer's Amyloid Precursor Protein by the Transmembrane Aspartic Protease BACE," Science, Vol. 286, 22 October 1999	
		Wang, Hoau et al. "Attenuated Protein Kinase C Activity and Translocation in Alzheimer's Disease Brain," Neurobiology of Aging, Vol. 15, No. 3, pp. 293-298, 1994	

Examiner Signature	Date Considered
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Substitute for form 1449/PTO

**INFORMATION DISCLOSURE
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Sheet	8	of		Application Number	10/519,110
				Filing Date	July 2, 2003
				First Named Inventor	Etcheberrigaray
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		Webb, Benjamin L.J., et al. "Protein kinase C isoenzymes: a review of their structure, regulation and role in regulating airways smooth muscle tone and mitogenesis," British Journal of Pharmacology (2000) 130, 1433-1452	
		Wiltfang, Jens et al. "Molecular Biology of Alzheimer's Dementia and Its Clinical Relevance to Early Diagnosis and New Therapeutic Strategies," Gerontology 2001; 47:65-71	
		Xu, Huaxi et al. "Metabolism of Alzheimer B-Amyloid precursor protein: Regulation by protein kinase A in intact cells and in a cell-free system," Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 4081-4084, April 1996	
		Zhang, Xueshu et al. "Preclinical Pharmacology of the Nature Product Anticancer Agent Bryostatins 1, an Activator of Protein Kinase C1," Cancer Research 56, 802-808, February 1996	

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